greater than 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.--

--50. (New) The method of Claim 1 in which the patient has had previous vascular surgery, or is undergoing current vascular surgery, or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level greater than 6.2 mmol/L, or diabetes mellitus.--

--51. (New) The method of Claim 1 in which the agent is atenolol and the maximum effective dose is about 100 mg/day orally or about 10 mg BID intravenously.--

--52. (New) The method of Claim 1 in which the agent is administered daily in the period after surgery until reduction of symptoms of cardiovascular stress is seen.--

REMARKS

Upon entry of the present Amendment, Claims 1-16 and 49-52 are pending and under consideration. A clean copy of the claims as currently pending is attached hereto as Appendix A.

I. THE AMENDMENTS

Claims 17-48 have been canceled without prejudice to Applicant's right to pursue the canceled subject matter in any related applications. Claims 1-4 have been amended, and new Claims 49-52 have been added. The new claims and the amendments are fully supported by the specification and claims as originally filed. In particular, support for the amendment to Claim 1 can be found in the specification at, for example, page 13, line 16, through page 14, line 12, disclosing a method of continuously administering a pharmacologic cardiovascular agent near its maximum effective dose to a patient following surgery. The specification teaches administration of the agent while the patient's heart rate is greater than 65 bpm and systolic blood pressure is greater than 100 mm Hg (*see* specification at page 14, lines 7-12) and while the patient shows no evidence of congestive heart failure, third degree heart block, or bronchospasm (*see* specification at page 13, lines 24-28). The term "maximum effective dose" is known to one of skill in the art of medicine and particularly the

art of cardiovascular agents. One of skill in the art would recognize that the specification teaches administration of atenolol, for example, near its maximum effective dose of about 100 mg/day (*see* specification at page 14, lines 7-9; *see also* Physician's Desk Reference and Goodman and Gilman's, The Pharmacological Basis of Therapeutics, both incorporated by reference in the specification at page 20, lines 23-24). The specification also teaches administration of numerous other cardiovascular agents near their maximum effective doses (*see* specification at page 9, line 25, through page 10, line 15). Daily administration of the agent is taught in the specification at page 12, lines 18-20. Claims 2-4 have been similarly amended to recite daily administration of an agent.

New Claim 49 is supported by the specification at page 13, line 16, through page 14, line 12. New Claim 50 is supported by the specification at page 11, line 28, through page 12, line 2, and by Mangano *et al.*, JAMA 268:233-239 (incorporated by reference in the specification at page 12, line 32, and at page 20, lines 23-24). The amendment to the specification is also supported by Mangano *et al.*, JAMA 268:233-239. New Claim 51 is supported by the specification at page 9, lines 25-26. New Claim 52 is supported by the specification at page 12, lines 18-20.

As the amendments are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry of the amendments is therefore respectfully requested.

II. THE INVENTION

The invention relates to methods for reducing mortality and cardiovascular morbidity following surgery. More than one million patients undergoing noncardiac surgery suffer heart attacks or other cardiac complications after surgery, with about 500,000 resultant deaths during the first two postoperative years. In patients with or at risk for coronary artery disease, myocardial ischemia or non-fatal myocardial infarction occurring during the first week following surgery increases the risk of serious adverse cardiovascular outcomes by 2- to 20-fold over the two years following surgery. Postoperative ischemia has been associated with an elevated heart rate response following surgery.

The present invention provides methods for reducing mortality and cardiovascular morbidity following surgery by the intraoperative and postoperative administration of an aggressive amount of a pharmacologic cardiovascular agent. In

particular, the invention relates to the intensive postoperative administration of such an agent during hospitalization and even after hospital discharge to mitigate the sympathetic response associated with increased heart rate, increased thrombosis and increased inflammatory response, thereby reducing the incidence and/or severity of cardiovascular complications such as myocardial infarction, unstable angina, congestive heart failure, dysrhythmia, myocardial revascularization, and death.

The invention is based, in part, on the Applicant's discovery that the aggressive administration of a β-adrenergic blocker, atenolol, prior to and immediately following surgery, and continuing daily throughout the entire period of hospitalization in patients with, or at risk for, coronary artery disease undergoing noncardiac surgery, reduces mortality and serious cardiovascular complications following hospital discharge, with the early survival effects persisting for two years.

III. ELECTION OF SPECIES

In an Office Action dated December 8, 1999, the Examiner indicated that Claims 1-48 are generic to a plurality of disclosed patentably distinct species comprising pharmacologic cardiovascular agents and required election of a single disclosed species under 35 U.S.C. § 121. Applicant elects the pharmacological cardiovascular agent atenolol of amended Claim 6. Amended Claims 1-6 and 15-16 and new Claims 49-52 read on the elected species.

Applicant understands that the election is being made solely to facilitate examination of the application, and that Applicant is entitled to consideration of additional species that are encompassed within the present generic claims.

IV. PREVIOUS REJECTIONS

In an Office Action mailed April 22, 1999 in the parent 08/631,334 application Serial No. 08/787,056, Claims 1-16 were rejected on various grounds. In the interest of expediting prosecution, Applicant addresses each rejection in view of the amended claims.

A. Rejections Under 35 U.S.C. § 102

Claims 1-16 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by each of White *et al.*, Derwent No. 84-54432 ("White"), Merrick *et al.*, LMS Drug Alerts 00429516 ("Merrick"), Lamb *et al.*, LMS Drug Alerts 00012889 ("Lamb"),

Matangi *et al.*, LMS Drug alerts 00017573 ("Matangi"), Kataria *et al.*, EMBASE NO. 90389658 ("Kataria"), Bojar *et al.*, EMBASE No. 88218301 ("Bojar"), Gray *et al.*, JAMA 56:49F-54F, 1985 ("Gray"), Smulyan *et al.*, JAMA 247:2539-42, 1982 ("Smulyan"), and Reves' *et al.*, JAMA 56:57F-60F, 1985 ("Reves"). Applicant traverses the rejections.

The standard for anticipation under 35 U.S.C. § 102 is strict identity. Anticipation under § 102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.* 223 USPQ 1264 (1984). None of the references teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Claim 1, and Claims 2-16 and 50-52 which depend therefrom, recite a method for reducing cardiovascular disease complications in a patient following surgery that comprises intensive administration of a cardiovascular agent. Independent Claim 49 comprises a similar method. Quite significantly, the methods comprise daily administration of the cardiovascular agent near its maximum effective dose while the patient's heart rate is greater than or equal to 65 bpm and the patient's systolic blood pressure is greater than or equal to 100 mm Hg and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. The method of Claim 49 additionally comprises administration of the agent at a reduced dosage when the patient's heart rate is greater than or equal to 55 bpm but less than 65 bpm.

None of the references cited by the Examiner teaches each and every element of Claims 1-16, as amended, and new Claims 49-52.

White teaches the administration of timolol to patients following surgery in a seven day clinical trial to show the safety and efficacy of timolol in reducing the severity of arrythmias. White fails to teach the daily administration of a cardiovascular agent near its maximum effective dose. White neglects to even report the dose of timolol administered in the trial. White also fails to teach the administration of the agent while the patient's heart rate is greater than or equal to 65 bpm and the patient's blood pressure is greater than or equal to 100 mm Hg. White therefore fails to teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Merrick teaches the administration of atenolol, a cardiovascular agent, at a dose of 50 mg/day while the patient's heart rate is greater than 80 bpm and blood pressure is greater than 110 mm Hg. Merrick's conservative dosage of atenolol teaches away from the

aggressive therapy of the present invention. In addition, Merrick teaches the oral administration of atenolol following surgery only when the patient is able to take oral medication. Since Merrick does not teach, and teaches away from, the administration of the agent when the patient is not able to take oral medication, Merrick does not teach the daily administration of an agent in the full period following surgery. Finally, Merrick does not teach the administration of a cardiovascular agent when the patient's heart rate is as low as 65 bpm and systolic blood pressure is as low as 100 mm Hg. Merrick therefore does not teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Lamb teaches the administration of 50 mg/day of atenolol to patients following surgery. Like Merrick, Lamb also teaches a conservative dose of atenolol that is significantly less than the near maximum dose recited in Claims 1-16, as amended, and new Claims 49-52. Hence, Lamb also teaches away from an aggressive dose of a cardiovascular agent. Lamb also teaches the administration of an oral dose of atenolol only and thereby teaches away from the administration of an agent in any period following surgery while the patient is not able to take oral medication. In addition, Lamb does not teach any of the exclusion conditions recited in Claims 1-16, as amended, and new Claims 49-52 such as heart rate, blood pressure, and evidence of congestive heart failure, third degree heart block, or bronchospasm. Lamb therefore does not teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Matangi teaches the administration of atenolol to patients following surgery. However, Matangi teaches a conservative dose of atenolol, 5 mg/day by intravenous infusion followed by 50 mg/day orally. Matangi teaches away from the daily administration of a cardiovascular agent near its maximum effective dose. In addition, Matangi does not teach the criteria for exclusion of therapy recited in Claims 1-16, as amended, and new Claims 49-52. Matangi does not teach the administration of a cardiovascular agent while a patient's heart rate is as low as 65 bpm and blood pressure is as low as 100 mm Hg as recited in Claim 1-16, as amended, and new Claims 49-52. In fact, Matangi neglects to teach any measurement of heart rate at all as a guideline for therapy. Matangi therefore does not teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Kataria teaches reduction of hypertension following surgery by the administration of a dose esmolol to patients following surgery when their systolic blood pressure is greater than or equal to 150 mm Hg, diastolic blood pressure is greater than or

equal to 95 mmHg, and heart rate is greater than or equal to 70 bpm. Esmolol has a half-life in the body of about nine minutes, requires constant monitoring, and is not appropriate for daily administration in the period following surgery. In fact, the method taught by Kataria is a "fast-acting, short-lasting" method to control hypertension (*see* Kataria). The average infusion taught by Kataria is just 63.6 minutes. As such, Kataria short-lasting intravenous therapy teaches away from the daily administration of a cardiovascular agent in the period following surgery. In addition, Kataria does not teach, and in fact teaches away from, the aggressive administration of a cardiovascular agent to a patient daily while the patient's systolic blood pressure is as low as 100 mm Hg or while the patients heart rate is as low as 65 bpm. Kataria therefore does not teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Bojar speculates that labetalol might be effective for managing postoperative hypertension. Bojar does not teach the daily administration of a cardiovascular near its maximum effective dose following surgery. Bojar does not even provide a dosage of labetalol for treating hypertension. In addition, Bojar teaches none of the exclusion conditions of Claims 1-16, as amended, and new Claims 49-52 such as heart rate, blood pressure, and evidence of congestive heart failure, third degree heart block, or bronchospasm. Bojar therefore does not teach each and every element of Claims 1-16, as amended, and new Claims 49-52.

Gray teaches the reduction of hypertension in patients following cardiac surgery by administration of esmolol or nitroprusside. The teaching of Gray provides patients increasing doses of esmolol and nitroprusside only until the administration of the agent reaches a maximum allowable dosage. The increasing doses of Gray fall far short of daily administration of the maximum allowable dose of an agent. Gray therefore teaches away from the daily administration of an agent near its maximum effective dose. In addition, the method taught by Gray required that patients exhibit a systolic blood pressure of at least 140 mm Hg prior to administration of esmolol. Gray further teaches that administration of esmolol or nitroprusside is stopped after the patient reaches a 15% decrease in systolic arterial pressure or a systolic pressure of less than or equal to 120 mm Hg. Gray thus teaches away from the daily administration of a cardiovascular agent to patients whose systolic blood pressure is as low as 100 mm Hg as recited in Claims 1-16, as amended, and new Claims 49-

52. Gray therefore does not teach each and every element of Claims 1-16, as amended, or new Claims 49-52.

Smulyan teaches the maintenance of propranolol infusion following abdominal surgery. Smulyan's describes the dosage of propranolol as "subtherapeutic" (*see* Smulyan at page 2541). As such, Smulyan does not teach the administration of cardiovascular agent near its maximum effective dose and in fact teaches away from such a dose. In addition, Smulyan does not teach daily administration of the maximum effective dose of a cardiovascular agent while the patient's heart rate is greater than or equal to 65 bpm and systolic blood pressure is greater than or equal to 100 mm Hg. Smulyan therefore does not teach each and every element of Claims 1-16, as amended, or new Claims 49-52.

Finally, Reves teaches the perioperative use of esmolol. Esmolol is an "ultrashort-acting parenteral β-adrenergic antagonist with a half-life of 9 minutes" (*see* Reves at page 57F). Reves reviews other studies which administered esmolol to dogs at infusion rates of up to 3000 μg/kg/min for 20 minutes or to humans at infusion rates of up to 300 ug/kg/min for 10 minutes. Some human studies reviewed by Reves include loading doses of esmolol of up to 500 μg/kg/min. As noted above, esmolol is not appropriate for daily administration in the period following surgery because of its short half-life and requirement of constant monitoring. In fact, the longest infusion of esmolol taught by Reves lasts just 20 minutes. As a result, Reves does not teach the daily administration of a cardiovascular agent near its maximum effective dose. In addition, Reves teaches no conditions for the exclusion of therapy such as heart rate, blood pressure, and evidence of congestive heart failure, third degree heart block, or bronchospasm. Reves therefore does not teach each and every element of Claims 1-16, as amended, or new Claims 49-52.

For the reasons stated above, Applicant submits that White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves do not anticipate Claims 1-16, as amended, or new Claims 49-52. Applicant respectfully requests that the rejections of Claims 1-16 under U.S.C. § 102 be withdrawn. Applicant also submits that new Claims 49-52 meet the requirements for patentability under 35 U.S.C. § 102.

B. <u>The Rejections under 35 U.S.C. § 103(a)</u>

Claims 1-16 were rejected in the alternative under 35 U.S.C. § 103(a) as allegedly being obvious over any of White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves in view of Wang *et al.*, EMBASE No. 83085294 ("Wang"), Goodman

and Gilman ("Goodman"), and Physician's Desk Handbook ("PDR"). Although the Examiner admits that White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves do not teach other cardiovascular agents instead of β-blockers, the Examiner contends that it would have been *prima facie* obvious to use other known cardiovascular agents in management of cardiovascular complication after surgery. Applicant traverses the rejection.

When rejecting claims under 35 U.S.C. § 103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). Three criteria are required to establish a *prima facie* case of obviousness. First, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *See* MPEP § 706.02(j). Second, when an obviousness determination relies on one reference, the Examiner must produce some suggestion or motivation to modify the teaching of the reference in the manner suggested by the Examiner. *See, e.g., In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). When an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references may be found in teachings within the references themselves, the ordinary knowledge of those of skill in the art, or the nature of the problem to be solved. *See id.* Finally, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. *See, e.g., In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). The reasonable expectation of success must be found in the prior art, not in the Applicant's disclosure. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Claims 1-16, as amended, and new Claims 49-52 are not obvious for substantially the same reasons discussed above. Claims 1-16, as amended, and new Claims 49-52 recite methods of reducing cardiovascular disease complications comprising the daily administration of a cardiovascular agent near its maximum effective dose following surgery. The methods also recite administering the agent while the patient's heart rate is greater than or equal to 65 bpm, the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

As discussed above, none of White, Merrick, Lamb, Kataria, Bojar, Smulyan, and Reves teach or suggest the daily administration of a cardiovascular agent near its maximum effective dose following surgery. The combination of any of these references and Wang, Goodman, and PDR also fails to teach or suggest the daily administration of a cardiovascular agent near its maximum effective dose following surgery. Wang teaches that certain categories of drugs affect the cardiovascular system. Wang does not teach or suggest the daily administration of a cardiovascular agent near its maximum effective dose following surgery. Goodman teaches certain cardiovascular agents including ACE inhibitors, calcium-channel blockers, and β-andrenergic antagonists. Goodman does not teach or suggest the daily administration of a cardiovascular agent near its maximum effective dose following surgery. Finally, PDR teaches a plethora of drugs including numerous cardiovascular agents. PDR also does not teach or suggest the daily administration of a cardiovascular agent near its maximum effective dose following surgery. As a result, the combination of any of White, Merrick, Lamb, Bojar, and Smulyan with Wang, Goodman, and PDR does not teach or suggest each and every element of Claims 1-16, as amended, and new Claims 49-52.

As discussed above, none of White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves teaches or suggests administering a cardiovascular agent while the patient's heart rate is greater than or equal to 65 bpm, the patient's blood pressure is greater than or equal to 100 mm Hg, and the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. The combination of any of these references and Wang, Goodman, and PDR also fails to teach or suggest administering a cardiovascular agent while the patient's heart rate is greater than or equal to 65 bpm, the patient's blood pressure is greater than or equal to 100 mm Hg, and the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. Neither Wang, Goodman, nor PDR teaches or suggests administering a cardiovascular agent while the patient's heart rate is greater than or equal to 65 bpm, the patient's blood pressure is greater than or equal to 100 mm Hg, and the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. As a result, the combination of any of White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves with Wang, Goodman, and PDR does not teach or suggest each and every element of Claims 1-16, as amended, or new Claims 49-52.

As a result, the combination of any of White, Merrick, Lamb, Matangi, Kataria, Bojar, Gray, Smulyan, and Reves with Wang, Goodman, and PDR fails to teach or

suggest each and every element Claims 1-16, as amended, and new Claims 49-52. The Examiner has thus failed to make out a *prima facie* case of obviousness for amended Claims 1-16. Applicant respectfully requests that the rejections of Claims 1-16 under 35 U.S.C. § 103(a) be withdrawn. Applicant also submits that new Claims 49-52 meet the requirements for patentability under 35 U.S.C. § 103(a).

V. CONCLUSION

Applicant submits that Claims 1-16 and 49-52 meet all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-16 and 49-52 to issuance is therefore kindly solicited. The Examiner is also invited to telephone the undersigned should the Examiner believe a telephone conference could expedite prosecution of the instant claims.

Applicant estimates that no fee is due with this response. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to the deposit account No. 16-1150 for any matter in connection with this response which may be required.

Respectfully submitted,

By #42,983

Date: January 7, 2000

30,605

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Appendix A
Claims After Entry of Amendment

1. A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent after surgery near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm wherein the pharmacologic agent is administered daily in the period after surgery.

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2. The method of Claim 1 in which the agent is administered daily in the period after surgery until hospital discharge.

3. The method of Claim 2 in which the agent is administered daily in the period after surgery for at least three days.

4. The method of Claim 2 in which the agent is administered daily in the period after surgery for up to seven days.

5. The method of Claim 1 in which the agent is a β_1-adrenergic selective blocking agent.

6. The method of Claim 5 in which the agent is atenolol.

7. The method of Claim 1 in which the agent is an α-2 agonist.

8. The method of Claim 1 in which the agent is a nitrate.

9. The method of Claim 1 in which the agent is a calcium channel blocker.

10. The method of Claim 1 in which the agent is an ACE inhibitor.

11. The method of Claim 1 in which the agent is a platelet inhibitor.

12. The method of Claim 1 in which the agent is a thrombosis inhibitor.

13. The method of Claim 1 in which the surgery is cardiac-related surgery.

14. The method of Claim 1 in which the surgery is non-cardiac-related surgery.

15. The method of Claim 1 in which the patient suffers from coronary artery disease.

16. The method of Claim 1 wherein the patient is at risk for coronary artery disease.

49. A method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: continuously administering to the patient a pharmacologic cardiovascular agent after surgery wherein the agent is

a) continuously administered near the maximum effective dose of the agent while the patient's heart

rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm; and

b) continuously administered at about one half of the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 55 bpm, but less than 65 bpm, while the patient's systolic blood pressure is greater than 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

50. The method of Claim 1 in which the patient has had previous vascular surgery, or is undergoing current vascular surgery, or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least 6.2 mmol/L, or diabetes mellitus.

51. The method of Claim 1 in which the agent is atenolol and the maximum effective dose is about 100 mg/day orally or about 10 mg BID intravenously.

52. The method of Claim 1 in which the agent is administered daily in the period after surgery until reduction of symptoms of cardiovascular stress.